SUPPORT FOR THE AMENDMENTS

The present amendment amends claims 23 and 28.

Support for the amendment to claims 23 and 28 is found at specification page 2, lines 8-10 and 21-22, page 4, lines 22-26, page 5, lines 6-20, page 12, lines 1-5, Example 1, Figures 1 and 2, as well as original claims 23 and 28.

It is believed that these amendments have not resulted in the introduction of new matter.

REMARKS

Claims 23-33 are currently pending in the present application. Claims 23 and 28 have been amended by the present amendment.

The rejection of claims 23-33 under 35 U.S.C. § 103(a) as being obvious over Kodama '169 (U.S. Patent 6,498,169) in view of Bicknell (Tumour Angiogenesis), as evidenced by Bischoff (Journal of Clinical Investigation) and Tei (Cancer Research), is respectfully traversed in part, and obviated by amendment in part.

Amended claim 23 recites, in part, a method for inhibiting angiogenesis comprising: administering to *a patient in need thereof an effective amount of a cyclic amine compound for inhibiting vascular endothelial growth factor-A (VEGF-A)*, wherein the cyclic amine compound is represented by the general formula (1); and inhibiting angiogenesis by inhibiting VEGF-A with the cyclic amine compound.

Kodama '169, Bicknell, Bischoff and Tei, when considered alone or in combination, fail to disclose or suggest a method for inhibiting angiogenesis comprising administering to *a patient in need thereof an effective amount of a cyclic amine compound for inhibiting VEGF-A*, wherein the cyclic amine compound is represented by the general formula (1), and inhibiting angiogenesis by inhibiting VEGF-A with the cyclic amine compound, as claimed in claim 23.

Amended claim 28 recites, in part, a method for treating a disease or pathological condition caused by angiogenesis comprising: administering to *a patient in need thereof an effective amount of a cyclic amine compound for inhibiting vascular endothelial growth factor-A (VEGF-A)*, wherein the cyclic amine compound is represented by the general formula (1); and inhibiting angiogenesis by inhibiting VEGF-A with the cyclic amine compound, thereby treating the disease or pathological condition caused by angiogenesis.

Kodama '169, Bicknell, Bischoff and Tei, when considered alone or in combination, also fail to disclose or suggest a method for treating a disease or pathological condition caused by angiogenesis comprising administering to *a patient in need thereof an effective amount of a cyclic amine compound for inhibiting VEGF-A*, wherein the cyclic amine compound is represented by the general formula (1), and inhibiting angiogenesis by inhibiting VEGF-A with the cyclic amine compound, thereby treating the disease or pathological condition caused by angiogenesis, as claimed in claim 28.

Kodama '169 describes that cyclic amine compounds represented by general formula (1) exhibit inhibitory effects on endothelial cell adhesion and are useful for treating inflammatory diseases (See e.g., abstract, column 1, lines 11-18 and 40-54, column 2, lines 56-67, column 3, lines 1-49, column 118, Test Example 1, column 119, Table 1 and lines 36-44, column 20, lines 26-31). Kodama '169 describes a trihydrochloride salt of 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine and a trihydrochloride salt 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (See e.g., column 47, Example 10, and column 53, Example 13).

Bicknell hypothesizes that tumor growth may be angiogenesis dependent and describes that angiogenesis is a complex process involving many prominent sequential steps including, but not limited to, the release of proteases from activated endothelial cells, extracellular matrix (ECM) degradation, and endothelial cell migration, proliferation and alignment (See e.g., columns 1 and 2).

Bischoff describes that during angiogenesis endothelial cells degrade the ECM, then migrate, proliferate, align themselves and adhere to one another to construct and extend new microcapillaries (See e.g., page 373, column 1, lines 21-33, page 373, column 2, lines 1-8 and

30-35). Bischoff describes that aberrant angiogenesis occurs in various pathologies and diseases including chronic inflammatory diseases, solid tumors and diabetic retinopathy (See e.g., page 373, column 1, lines 7-11).

Tei describes that tumor angiogenesis is highly dependent on the action of cell adhesion molecules (e.g., integrins) mediating the adhesion of cancer cells to endothelial cells (See e.g., abstract, page 6295, column 1, last line, page 6295, column 2, lines 1-6 and 12-15).

Kodama '169, Bicknell, Bischoff and Tei, when considered alone or in combination, fail to disclose or suggest inhibiting VEGF-A by administering to a patient in need thereof an effective amount of a cyclic amine compound of formula (1), as presently claimed.

The claimed methods, which comprise administering to a patient in need thereof an effective amount of a cyclic amine compound of formula (1) for inhibiting VEGF-A, are properly construed, based on the plain meaning of the claims and the prosecution history of this case, to require that an effective amount of the cyclic amine compound of formula (1) be administered to a patient with a recognized need to inhibit VEGF-A.

Based on established U.S. case law, in order for Kodama '169, Bicknell, Bischoff and/or Tei to render obvious the claimed methods, these references must provide a skilled artisan with sufficient motivation and guidance to administer an effective amount of the cyclic amine compound of formula (1) to a patient with the intent of inhibiting VEGF-A. See e.g., *Jansen v. Rexall Sundown Inc.*, 68 USPQ2d 1154 (Fed. Cir. 2003). Contrary to the Official Action, administering the claimed cyclic amine compound of formula (1) for some purpose other than inhibiting VEGF-A is not practicing the claimed method. *Id.* at 1158. Since Kodama '169, Bicknell, Bischoff and Tei fail to disclose or suggest administering the cyclic amine compound of formula (1) to a patient with a recognized need to inhibit VEGF-A, these references fail to render obvious the methods of the present invention.

Assuming *arguendo* that sufficient motivation and guidance is considered to have been provided by Kodama '169, Bicknell, Bischoff and/or Tei to direct a skilled artisan to arrive at the methods of the present invention comprising inhibiting VEGF-A by administering to a patient in need thereof an effective amount of a cyclic amine compound of formula (1), which is clearly not the case, such a case of obviousness is rebutted by a showing of unexpected results.

As previously mentioned, Kodama '169 describes that cyclic amine compounds represented by general formula (1) exhibit inhibitory effects on *endothelial cell adhesion* and are useful for treating inflammatory diseases. As acknowledged by the combined disclosures of Bicknell, Bischoff and Tei, angiogenesis is a ***complex process*** involving many sequential steps including, but not limited to, the release of proteases from activated endothelial cells, and *endothelial cell* migration, proliferation, alignment and *adhesion*.

Unlike inhibiting *endothelial cell adhesion* for treating inflammatory diseases and tumor angiogenesis, as described in the combined disclosures of Kodama '169, Bicknell, Bischoff and Tei, Applicants have discovered that the claimed cyclic amine compounds represented by general formula (1) *unexpectedly* exhibited inhibitory effects on *VEGF-A*, thereby inhibiting angiogenesis and/or treating a disease or pathological condition caused by angiogenesis, in accordance with the methods of the present invention.

Unlike the *endothelial cell adhesion* of Kodama '169, Bicknell, Bischoff and Tei, vascular endothelial growth factor-A (VEGF-A) is a signaling protein involved in stimulating *endothelial cell migration and proliferation* and a factor associated with the initial stage of angiogenesis *prior to adhesion between endothelial cells*. None of the cited references disclose or suggest that that the cyclic amine compounds of formula (1) exhibit an inhibitory effect on VEGF-A.

Although some compounds inhibit angiogenesis by exhibiting inhibitory effects on endothelial cell adhesion, not all angiogenesis inhibitors exhibit inhibitory effects on endothelial cell adhesion. For example, maspin is a *protease inhibitor* that inhibits angiogenesis by exhibiting inhibitory effects on endothelial cell *migration*; vasostatin, calreticulin, prothrombin and antithrobin III are angiogenesis inhibitors that exhibit inhibitory effects on endothelial cell *proliferation*; while angiostatin and VEGI are angiogenesis inhibitors that induce *apoptosis* of endothelial cells.

In addition, not all angiogenesis inhibitors that exhibit inhibitory effects on vascular endothelial growth factor (VEGF) necessarily exhibit inhibitory effects on endothelial cell adhesion. For example, VEGF-Trap is a decoy receptor substance that inhibits angiogenesis by binding to and inactivating VEGF; bevacizumab is a monoclonal antibody that inhibits angiogenesis by binding to and inactivating VEGF; and sunitinib is a VEGF receptor tyrosine kinase (RTK) inhibitor that inhibits angiogenesis by disrupting VEGF receptor-mediated signaling. However, it is unknown whether these anti-VEGF angiogenesis inhibitors exhibit inhibitory effects on endothelial cell adhesion.

Accordingly, contrary to the Examiner's assertion, it would not have been obvious to a skilled artisan that the cyclic amine compounds of formula (1), which exhibit inhibitory effects on endothelial cell adhesion, would exhibit an inhibitory effect on VEGF-A, as presently claimed.

It is improper to selectively consider evidence and disregard evidence that favors patentability. *In re Piasecki*, 223 USPQ 785 (Fed. Cir. 1984).

As evidenced by the experimental data presented in Example 1 and Figures 1 and 2 of the present specification, as well as Figure A of the previously submitted Declaration under 37 C.F.R. § 1.132, Applicants have discovered that the claimed cyclic amine compounds represented by general formula (1) *surprisingly* exhibited inhibitory effects on VEGF-A,

thereby inhibiting angiogenesis and/or treating a disease or pathological condition caused by angiogenesis, in accordance with the methods of the present invention.

Withdrawal of this ground of rejection is respectfully requested.

The nonstatutory obviousness-type double patenting rejections of claims 23-33 as being unpatentable over claims: (1) 15-20 of Kodama '169 (U.S. Patent 6,498,169) in view of Bicknell (Tumour Angiogenesis); (2) 13-17 of Kodama '753 (U.S. Patent 6,395,753) in view of Bicknell; (3) 3 of Kodama '620 (U.S. Patent 6,605,620) in view of Bicknell; and (4) 13-17 of Kodama '221 (U.S. Patent 6,867,221) in view of Bicknell, are respectfully traversed in part, and obviated by amendment in part, for the same reasons as discussed above.

Withdrawal of these grounds of rejection is respectfully requested.

The rejection of claims 23-33 under 35 U.S.C. § 112, first paragraph (scope of enablement), is obviated by amendment.

Withdrawal of this ground of rejection is respectfully requested.

In conclusion, Applicants submit that the present application is now in condition for allowance and notification to this effect is earnestly solicited.

Respectfully submitted,

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